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SAĞLIKLI VE GESTASYONEL DİABETES MELLİTUSLU GEBELERİN D VİTAMİNİ SEVİYELERİNİN KARŞILAŞTIRILMASI

THE COMPARISON OF VITAMIN D LEVELS OF HEALTHY AND GESTATIONAL DIABETIC PREGNANT WOMEN

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Öz

Amaç: Bu çalışmadaki amacımız; gestasyonel diyabetes mellitus (GDM) olan gebelerle normal glukoz toleransı (NGT) olan gebelerin 25 hidroksi vitamin D [25(OH)D3] seviyelerini karşılaştırmaktır. Gereç ve Yöntem: Vaka kontrollü prospektif bir araştırma olan bu çalışmaya kadın hastalıkları ve doğum polikliniğine 24-28. haftalarında kontrole gelen ve 50 ve/veya 100 gr OGTT testi yapılan 40 gebe (20 GDM ve 20 sağlıklı kontrol grubu) dahil edildi. American College of Obstetricians and Gynecologists (ACOG) kriterlerine göre GDM ve kontrol grubu belirledi. Gebelerin yaşları, boy ve kiloları, beden kitle indeksleri (BKİ)'leri, geçirdiği hastalık ve ameliyat öyküsü, D vitamini kullanım öyküsü, giyim tarzları, egzersiz yapma durumları, ailede diyabet öyküsü kaydedildi. 25(OH)D3 ölçümü için gebelerin serum örnekleri 24-28. haftalarda alındı ve 25(OH)D3 düzeyi kemiluminans (chemiluminescence) tekniği ile ölçüldü. Bulgular: Tespit edilen ortalama 25(OH)D3 seviyesi 8.71±3.36 ng/mL (4.20 ile 18.84 arası) idi. Gebelerde %70 D vitamini eksikliği (<10 ng/ml), %30 D vitamini yetmezliği (10-30 ng/ml) mevcuttu. GDM tespit edilen grupta 25(OH)D3 seviyesi 9.40±3.53ng/ml, kontrol grubunda 8.0±3.11 ng/ml idi. Hasta ve kontrol grubu arasında 25(OH)D3 seviyeleri açısından istatistiksel olarak fark bulunmadı. Tartışma: Yaptığımız çalışmaya göre 25(OH)D3 seviyesi GDM'li gebeler ve sağlıklı gebelerde benzer ve düşük bulundu. 25(OH)D3 düzeyinin GDM gelişimindeki rolünün ortaya konması için daha geniş kapsamlı, prospektif, randomize-kontrollü çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Anahtar Kelimeler

Gestasyonel Diyabetes Mellitus; Gebelik; D Vitamini Seviyesi

Abstract

Aim: To evaluate and compare 25-hydroxyvitamin D [25(OH)D3] levels of women with gestational diabetes mellitus (GDM) and those with normal glucose tolerance (NGT). Material and Method: A total of 40 women (20 with GDM and 20 with NGT) admitted to the clinic of obstetrics and gynecology due to follow-ups between the 24th and 28th gestational weeks and exposed to 50 and/or 100 gr oral glucose tolerance testing (OGTT) were enrolled into this prospective case-controlled study. Patients with GDM and controls with NGT were defined according to the 2013 criteria of the American College of Obstetricians and Gynecologists (ACOG). Age, height, weight, body mass index (BMI), history of previous diseases and surgeries, vitamin D replacement, clothing style (in this region 95% of participants dress in a style that prevents the sun from reaching skin) exercising status, and familial history were recorded. Serum samples were collected between the 24th and 28th gestational weeks to measure 25(OH)D3 levels via the chemiluminescence method. Results: Mean 25(OH)D3 levels were found as 8.71±3.36 ng/mL (ranging from 4.20 to 18.84). Vitamin D deficiency (<10 ng/mL) and insufficiency(10-30 ng/ml) were observed at the rate of 70% and 30%, respectively. 25(OH)D3 levels were 9.40±3.53ng/mL in patients with GDM and 8.0±3.11 ng/mL in controls with NGT. In terms of vitamin D deficiency, no statistically significant difference was found between the GDM and NGT groups. Discussion: 25(OH)D3 levels were found to be similar or lower in patients with GDM and those with NGT. We consider that prospective, randomized-controlled and comprehensive studies with larger populations are needed to illuminate the role of 25(OH)D3 levels in the development of GDM.

Keywords

Gestational Diabetes Mellitus; Pregnancy; Vitamin D Status

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Introduction

Gestational diabetes mellitus (GDM) is a disorder related to the various degrees in levels of carbohydrates intolerance determined for the first time during pregnancy [1]. The incidence of GDM has ranged from 1.4% to 14.0% in various studies performed in the USA, and the rate is increasing despite all preventive efforts [2,3,4]. In Turkey, the incidence of GDM ranges from 4.2% to 11.2% [5,6]. The prevalence of GDM is increasing in societies where the prevalence of type 2 diabetes mellitus (DM) is higher [7,8,4]. In addition, the rates of GDM vary between countries, depending on factors such as racial differences, mean maternal age, and weight [2]. While 5-10% of women with GDM were diagnosed with type 2 DM immediately after giving birth, 20-50% were diagnosed with the condition within 5-10 years following the birth, and 35-60% within 10-20 years [2]. Based on these findings, GDM is a significant risk factor for type 2 DM.

In addition to the role of vitamin D in bone and mineral metabolism, it has also been associated with many diseases [9]. Various studies have demonstrated that vitamin D is effective in insulin secretion, in glucose uptake into cells, and in preventing the development and progression of inflammation in pancreas β cells [10,11,12,13]. Although the literature contains many studies investigating the effects of vitamin D deficiency on the development of type 1 and 2 DM, there are not enough studies assessing the effects of vitamin D levels in GDM [14,15]. Therefore, further research is needed [14].

In the present study, we compared vitamin D levels in women diagnosed with GDM and those with normal glucose tolerance (NGT) by performing 50 and 100 gr of oral glucose tolerance test (OGTT).

Material and Method

Study population and parameters

An approval was obtained from the ethics board of Selcuk University for clinical research on 26 September 2013. The study was supported by the Konya Training and Research Hospital. Informed written consent was obtained from all participants based on the principles of the Helsinki Declaration and its later amendments.

The study was designed as prospective and case-controlled. Before commencing the study, power analysis was calculated using the Minitab 17.0 program in accordance with the study by Zhang et al. [20]. The power of the test was 0.82 when 40 samples were included.

The study was performed in the clinic of obstetrics and gynecology of Konya Training and Research Hospital between September and December 2013. During this period 247 pregnant women, aged 18-40, between the 24th and 28th gestational weeks were examined and 209 of them were accepted to perform OGTT. 20 women were diagnosed with GDM at the end of the OGTT.

The exclusion criteria were those with multiple pregnancies; pregestational DM; history of chronic disorders; using alcohol; an uncontrolled endocrinological disorder; a disease affecting vitamin D metabolism such as renal failure, liver disease, gastrointestinal resection, hypothyroidism, hyperthyroidism, or hyperparathyroidism; and those taking drugs affecting vitamin D metabolism, such as phenitoin, phenobarbital, or thyroid hormone. In the present study, after the GDM group was constituted, 20 pregnant women who had similar features with the GDM group, such as age, body mass index (BMI), clothing style, and exercise status, were included as the control group.

Participants' features such as age, date of the last menstruation, educational status, profession, BMI, history of previous disorders, family history of DM, gravidas, parity, history of abortus, type of accommodation, clothing style, and exercise status were evaluated. Then, systolic and diastolic blood pressures (BP) were manually measured in the sitting position after 15 minutes resting using an aneroid tension device (Erka, Istanbul, Turkey), and BP scores were recorded. Weight was measured with underwear and without shoes. Height was measured with a measuring tape. BMI was calculated as weight (kg) divided by height squared (m2). Fasting venous blood samples of 2 cc were drawn into EDTA tubes from the antecubital veins of participants for vitamin D measurements. After waiting 30 minutes, the samples were centrifuged at 2000 g for 10 to 15 minutes and stored at -80°C. After collecting all samples, 25(OH)D3 levels were measured by the same researcher using the chemiluminescence method with an Advia Centaur XP kit (Siemens, Germany). Serum 25(OH)D3 levels of ≤10 ng/mL were assessed as severe vitamin D deficiency; between 10-29.9 ng/mL as vitamin D insufficiency; and ≥30 ng/mL as sufficient vitamin D level [16].

Both the GDM and NGT groups were followed up until delivery. Mothers giving birth at other hospitals were followed up through telephone, and the information about all participants such as mode of delivery, whether there were complications or not, and the gender, birth weight, and height of the neonates were recorded. Four patients were not reached through telephone or hospital records after delivery.

Oral glucose tolerance testing

Under the 2013 criteria of the American College of Obstetricians and Gynecologists (ACOG), 50 and/or 100 gr oral glucose tolerance tests (OGTT) were performed as screening and diagnostic tests.

According to the thresholds defined by the 2013 Diabetes Guidelines of the Turkish Association of Endocrinology and Metabolism (TAEM) and the 2013 criteria of ACOG, 50 gr of oral glucose tolerance test (OGTT) was performed as the GDM screening test [8,31]. After 50 gr OGTT, pregnant women whose plasma glucose levels were ≤ 140 mg/dL at the 1st hour were enrolled as controls. Those with plasma glucose levels of ≥180 mg/dL at the 1st hour were assessed as pregnancies with GDM. 100 gr OGTT was performed for those with plasma glucose between 140-180 mg/dL at the 1st hour. 100 gr OGTT was performed after administering a carbohydrate-rich diet for three days and following 8 to 12-hour overnight fasting. Venous plasma levels were evaluated in all pregnant women. After 100 gr glucose was dissolved in 250 mL of water, and the patient was stable, venous plasma glucose levels were measured at the 1st, 2nd, and 3rd hours. Based on the thresholds of the 2013 Diabetes Guidelines of TAEM and the 2013 criteria of ACOG, plasma glucose levels of 95 mg/dL, 180 mg/dL, 155 mg/dL, and 140 mg/dL were established as the fasting plasma glucose cut-off levels for the 1st, 2nd, and 3rd hours, respectively. The participants who had two or more higher levels in these four parameters were accepted as those with GDM. Those with only one higher parameter were excluded.

Statistical Analysis

Data collection and statistical analyses were conducted through SPSS 21.0 software package (IBM Corp. Armonk, USA), and descriptive statistics and two sample T test were used for statistical calculations. For categorical data, the binominal ranking test was utilized. In order to determine the association between variables, the Pearson's correlation analysis was conducted. In all analyses, $p<0.05$ was accepted to be significant.

Results

The mean age of the study participants was 30.9±4.9 (21-40 years). The mean ages of pregnant women with GDM and NGT were found to be similar (31.3±4.9 and 30.5±4.9 years) ($p>0.05$). In the GDM and NGT groups, mean pregestational and the last weight rates, and mean pregestational BMI scores were similar ($p>0.05$).

In study participants, mean 25(OH)D3 levels were found as 8.71±3.36 ng/mL (ranging from 4.20 to 18.84). Vitamin D deficiency (<10 ng/mL) and insufficiency (10-30 ng/ml) were observed at the rate of 70% and 30%, respectively. When serum 25(OH)D3 levels were compared with vitamin D status, serum 25(OH)D3 levels were found to be 10.56±4.07 ng/mL in those taking vitamin D supplements and 7.47±2.09 ng/mL in those not taking. A significant difference was observed between these two parameters ($p=0.03$). However, 25(OH)D3 levels were under normal limits even in those taking vitamin D.

Serum 25(OH)D3 levels of GDM group and those with healthy pregnancies were detected as 9.4±3.5 ng/L and 8.0±3.1 ng/mL, respectively, and no statistically significant difference was found between these parameters ($p>0.05$) (Table 1).

In neither group was there an association between vitamin D levels and educational and employment status ($p>0.05$), or between vitamin D levels and systolic and diastolic BP ($r=-0.19$ $p=0.230$; $r=-0.20$ $p=0.21$).

Of participants with GDM, 55.6% were detected to give birth with normal spontaneous vaginal delivery (NSVD), 38.9% with cesarean section (C/S), and 5.6% with assisted vaginal delivery. In the NGT group, 52.9% and 47.1% were observed to give births via NSVD and C/S, respectively; none had births via assisted vaginal delivery. No statistically significant difference was determined between the groups ($p>0.05$). Of the neonates of women in GDM group, 61.1% were seen to be male, and 38.9% to be female; however, male and female neonates of women in NGT group were found to be 81.3% and 18.7%, respectively. No statistically significant difference was found between GDM and NGT groups ($p>0.05$).

In terms of birth weight and height, no difference was found between the neonates of mothers with GDM and healthy control mothers ($p>0.05$). In the study, the neonates were classified into two groups, as those with normal birth weight and macrosomic ones (3500 gr and over). While vitamin D levels were found to be 7.12±1.96 ng/mL in the neonates' mothers with birth weight over 3500 gr, the levels were detected as 9.81±3.74 ng/mL in those with neonates under 3500 gr, a statistically significant difference ($p=0.02$). Between those with GDM and controls, no difference was observed as to maternal age, profession, educational level, pregestational BMI, weight gain during pregnancy, history of familial DM, gravidas, parity, history of abortus, or mode of delivery (Table 2).

Table 1. Socio-demographic features of GDM and healthy control groups, and comparison of study parameters

Study parameters	GDM (n=20) Mean±SD (min-max)	NGT (n=20) Mean±SD (min-max)	p
Maternal age (years)	31.3±4.9 (21-39)	30.5±4.9 (23-40)	0.61
50 gr OGTT At first hour (mg/dL)	196.0±22.6 (180-212)	100.0±19.0 (59-136)	<0.001
100 gr OGTT			
At initial (mg/dL)	94.4±13.5 (73-115)	-	-
At first hour (mg/dL)	184.5±19.6 (130-212)		
At second hour (mg/dL)	166.6±29.0 (105-206)		
At third hour (mg/dL)	127.5±22.8 (95-179)		
Pregestational maternal weight (kg)	62.0±12.0	61.8±8.7	0.96
Pregestational maternal BMI (kg/m2)	25.7±4.7	23.7±3.9	0.15
The last maternal weight (kg)	69.1±12.9	68.8±8.0	0.91
25(OH)D3 level (ng/mL)	9.4±3.5(5.32-17.92)	8.0±3.1 (4.2-18.84)	0.19
Height of neonates (cm)	50.95±2.0 (47-55)	50.35±3.1 (43-56)	0.50
Weight of neonates (gr)	3324.4±425.0(2810-4260)	3334.1±500.4 (2600-4500)	0.95
Gravidas	3.35±1.76 (1-8)	2.72±1.07 (1-4)	0.27
Parity	1.80±1.40 (0-5)	1.30±0.86 (0-3)	0.21
History of abortus			
Yes	11 (55.0%)	23 (65.0%)	0.80
No	9 (45.0%)	7 (35.0%)	
History of familial DM	11 (55.0%)	8 (40.0%)	0.34
Yes	9 (45.0%)	12 (60.0%)	
No			
Vitamin D replacement			0.52
Yes	9 (45.0%)	7 (35.0%)	
No	11 (55.0%)	13 (65.0%)	
Professional status			
Working	2 (10.0%)	3 (15.0%)	0.63
Not working	18 (90.0%)	17 (85.0%)	
Educational level			
Primary school	10 (50.0%)	10 (50.0%)	0.46
Secondary school	5 (25.0%)	4 (20.0%)	
High school	4 (20.0%)	2 (10.0%)	
University	1 (5.0%)	4 (20.0%)	
Mode of delivery			
NSVD	10(55.6%)	9 (52.9%)	0.58
C/S	7 (38.9%)	8 (47.1%)	
Assisted VD	1 (5.6%)	0.0	
Gender of neonates			
Male	11(61.1%)	13 (81.3%)	0.20
Female	7 (38.9%)	3 (18.7%)	
Birth weight of neonates (gr)	3324.4±425.0	3334.1±500.4	0.95
Birth height of neonates(cm)	50.95±2.0	50.35±3.1	0.50

The data were presented as mean±standard deviation (minimum-maksimum) or number (%). GDM: Gestational diabetes mellitus, NGT: Normal glucose tolerance test, OGTT: Oral glucose tolerance test, BMI: Body mass index, 25(OH)D3: 25 hydroxy vitamin D, NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section

Table 2. Comparison between 25(OH)D_3 levels and study parameters

	n	25(OH)D_3 Mean±SD	p
Educational level			
High school and over	11	9.49±4.34	0.36
Secondary school and under	29	8.41±2.95	
Professional status			
House wife	35	8.86±3.5	0.38
Working	5	7.56±2.1	
Birth weight of neonates(gr)			
≥3500	12	7.12±1.96	0.02
< 3500	23	9.81±3.74	
Maternal age(years)			
30	23	8.48±3.35	0.69
>30	17	8.90±3.44	
Vitamin D replacement			
Yes	16	10.56±4.07	0.03
No	24	7.47±2.09	

The data were presented as mean±standard deviation number (%).
25(OH)D3: 25 hydroxy vitamin D

Discussion

Vitamin D insufficiency has been reported to be quite common in various ethnic populations, especially in pregnancy [23]. In pregnant women, vitamin D deficiency was determined as 96.25% in China [23], as 33% [24] and 48% [26] in Australia, and as 70.6% [25] in Iran. In general, vitamin D levels were found to be lower in pregnancy in Asian women, compared to European and American women [22,26]. Consistent with these findings, 25(OH)D3 levels were also found to lower in all our participants. There was vitamin D deficiency (<10 ng/mL) and insufficiency (10-30 ng/ml) at the rate of 70% and 30%, respectively. We consider that the reason for higher levels of vitamin D deficiency was related to the clothing style worn by 95% of study participants, which prevents sunlight from reaching the skin. Also, the fact that serum 25(OH)D3 levels were assessed in the third trimester in the present study could lead to findings of higher levels of vitamin D deficiency.

While some previous studies reported no findings in terms of whether women with pregnancy took vitamin D replacement or not, vitamin D replacement status was investigated in pregnant women enrolled into the present study. Serum 25(OH)D3 levels were found as 10.56±4.07 ng/mL in women taking vitamin D replacement, compared to 7.47±2.09 ng/mL in those not taking. Thus, vitamin D levels were found to be statistically significantly higher in those given vitamin D replacement (p=0.03). However, vitamin D levels were also low in the group in whom vitamin D replacement was performed. It is likely this was due to such factors as taking the supplements irregularly or insufficient dose levels.

In the present study where age, socio-demographic characteristics, and BMI values of participants were matched, serum 25(OH)D3 levels were assessed as 9.40±3.53 ng/mL in women with GDM, compared to 8.0±3.11 ng/mL in NGT. There was no statistically significant difference between the two groups. However, vitamin D levels were low in both groups. Note also that the GDM group was enrolled in the study in September and October, whereas the healthy controls were identified in November and December to match the age, socio-demographic features and BMI of participants. Constituting the control group at a closer time to winter (when there is less sunlight) may also have affected the findings in the study. In addition, while assessed in the first trimester in most studies, 25(OH)D3 levels were evaluated in the second trimester in the present study.

In the literature, there are numerous studies reporting that a rate lower than 25(OH)D3 in the first trimester increases the risk of developing GDM in the second trimester [10,22,19,2,14]. In a meta-analysis where 20 observational studies including 9209 participants were reviewed, a consistent relationship was found between vitamin D deficiency and increase in GDM development. However, it was concluded in this analysis that well-designed and randomized-controlled studies were needed "in order to say that vitamin D replacement should be performed to prevent the development of GDM" [20]. In the present study, confounding factors, such as exercising status of study participants, type of homes (house, flat, etc.), cigarette smoking, sleeping mode, and profession, were also questioned, but no significant association was found between vitamin D levels and such confounders.

The literature also contains studies that did not find an association between vitamin D deficiency and the risk of developing GDM [17,18].

In our study, the correlations between 50 and 100 gr OGTT results and serum 25(OH)D3 levels were also evaluated. As seen in Table 3, no correlation was observed between 50 and 100 gr OGTT results and serum 25(OH)D3 levels.

Vitamin D deficiency has been reported to be associated with increases in serious short- and long-term health challenges in neonates and an increase in gestational complications such as preeclampsia and hypertension [16,22,29]. In a review published in 2016, it was reported that vitamin D replacement carried out in pregnant women until delivery could decrease the risks of preeclampsia, lower birth weight, and preterm births [30]. No correlation was found between vitamin D levels and systolic and diastolic BP in our study.

According to the hyperglycemia and adverse pregnancy outcome (HAPO) study performed by the International Association of Diabetic Pregnancy Study Groups (IADPSG), the results of which were published in 2008, a significant association was reported between maternal hyperglycemia and macrosomia, hyperinsulinemia, neonatal hypoglycemia, and gender [27]. In the present study, no significant association was found between gender of neonates and mothers' glucose and 25(OH)D3 levels. Also different from the literature, no significant difference was present between the neonates of mothers with GDM and NGT in terms of birth weight in our study. However, the neonates of mothers with lower vitamin D levels were observed to have heavier birth weight. Serum 25(OH)D3 levels in the mothers of neonates with birth weight over 3500 gr were found to be 7.12±1.96 ng/mL, while the levels were detected as 9.81±3.74 ng/mL in those with neonates under 3500 gr (p=0.02) (Table 2).

In several studies, a significant increase was detected between maternal hyperglycemia and cesarean section [27,28]. In the present study, however, the rates of interventional vaginal delivery and cesarean section were not higher in the GDM group than in the NGT group. We consider that this arose from the fact that all women with GDM were well-followed up.

There were also some limitations in our study. Our case and control number is limited due to financial issues. Because the study was supported by the funds of the Konya Training and Research Hospital, we had to enroll the minimal number of pregnant women that met the power analysis. Only one measurement of 25(OH)D3 levels was taken within the third trimester, the vitamin D levels are not reflective of the whole pregnancy period. Multiple measurements taken during the pregestational period and the first trimester may give us more reliable results. It would be better to exclude the cases that took vitamin D replacement. In the study, vitamin D levels were determined to be quite low in both patients and healthy controls, and thus the role of vitamin D in the development of GDM was not precisely evaluated due to lack of a group with normal vitamin D levels. Enrollment of women with GDM in September-October 2013 and of healthy controls in November-December 2013 could have lead to obtaining lower vitamin D levels in controls. Including both groups into the study during the same period could have led to more balanced findings.

Conclusion

Vitamin D deficiency is a commonly encountered health challenge in Turkish society, and vitamin D replacement cannot be performed at a sufficient and effective level. In the present study, 25(OH)D3 levels of pregnant women with GDM were found to be similar to those with NGT. It is important to understand whether vitamin D deficiency is a factor increasing GDM risk in pregnant women. We consider that repeated vitamin D measurements within the pregestational period and first trimester could illuminate the association between vitamin D deficiency and GDM more explicitly. We consider that prospective and randomized-controlled studies with larger population are needed to assess the effects of ethnic differences and confounding factors in the regions where vitamin D deficiency is widespread.

Competing interests

The authors declare that they have no competing interests.

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